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IARC MONOGRAPHS PROGRAMME FINDS COMBINED ESTROGEN-PROGESTOGEN CONTRACEPTIVES AND MENOPAUSAL THERAPY ARE CARCINOGENIC TO HUMANS

An IARC Monographs Working Group has concluded that combined estrogen-progestogen oral contraceptives and combined estrogen-progestogen menopausal therapy are carcinogenic to humans (Group 1), after a thorough review of the published scientific evidence.

At the same time, the Working Group stressed that there is also convincing evidence that oral contraceptives have a protective effect against some types of cancer.

There are both beneficial and adverse effects for oral contraceptives and menopausal therapy. Each woman who uses these products should discuss the overall risks and benefits with her doctor.

The Working Group, comprising 21 scientists from 8 countries, was convened by the IARC Monographs Programme of the International Agency for Research on Cancer (IARC), the cancer research agency of the World Health Organization.

Major public health importance
"These new IARC Monographs volume 91 address exposures that are experienced daily by many millions of women world-wide," said Dr Peter Boyle, Director of IARC. "It is of enormous public health importance that we identify and understand the full range of effects of these products." Worldwide, more than 100 million women – about 10% of all women of reproductive age – currently use combined hormonal contraceptives. In addition, there has been widespread use of hormonal menopausal therapy: approximately 20 million women in developed countries at its peak around the year 2000.

ORAL CONTRACEPTIVES INCREASE RISK OF SOME CANCERS AND DECREASE RISK OF OTHERS

Use of OC's increases risk of breast, cervix and liver cancer...
There is a small increase in the risk of breast cancer in current and recent users of oral contraceptives. However, ten years after cessation of use, the risk appears to be similar to that in never-users. The risk of cervical cancer increases with duration of use of combined oral contraceptives. The risk of hepatocellular carcinoma is increased in long-term users of combined oral contraceptives in populations with low prevalences of hepatitis B infection and chronic liver disease – two major causes of human liver cancer.

... but decreases risk of endometrial and ovarian cancer
In contrast, the risks of endometrial and ovarian cancer are consistently decreased in women who used combined oral contraceptives. The reduction is generally greater with longer duration of use, and some reduction persists at least 15 years after cessation of use.

More work needed to assess risks and benefits
Because use of combined estrogen-progestogen contraceptives increases some cancer risks and decreases risk of some other forms of cancer , it is possible that the overall net public health outcome may be beneficial, but a rigorous analysis is required to demonstrate this. This should be done on a country-by-country basis and also consider the effects on non-malignant diseases.

COMBINED MENOPAUSAL THERAPY INCREASES RISK OF CANCER

Breast cancer and endometrial cancer are increased
Epidemiological studies consistently demonstrate an increased risk of breast cancer in women who used combined menopausal therapy. Largely confined to current or recent users, the risk increases with duration of use and exceeds that in women taking estrogen-only therapy. Endometrial cancer risks depend on the number of days that progestogens are included in the combined therapy. When progestogens are taken fewer than 10 days per month, the risk of endometrial cancer is increased, but when progestogens are taken daily, the risk is similar to that in women who never used hormonal therapy. There was not sufficient evidence to conclude that hormonal therapy has a protective effect at any cancer site.

Overall risks and benefits should be weighed carefully
Both beneficial and adverse effects other than cancer have been established for combined estrogen-progestogen menopausal therapy. As for oral contraceptives, a rigorous risk/benefit analysis would be useful to put the different effects in perspective and assess the overall consequences for public health.

WHAT IS NEW, AND WHAT DOES THIS MEAN FOR ME?

More cancer sites are targets of oral contraceptives
Previously, combined oral contraceptives had been determined to be carcinogenic to humans, but only primary liver cancer was specifically implicated. The Working Group concluded that combined oral contraceptives alter the risk of several common cancers in women. They increase a woman's risk of cervical cancer, breast cancer, and liver cancer. At the same time, they have a protective effect against endometrial cancer and ovarian cancer.

Menopausal therapy now "Carcinogenic to humans"
Previously, combined menopausal therapy was regarded as "possibly carcinogenic to humans." The new evaluation concluded, based on an expanded study base, that it is carcinogenic to humans, increasing a woman's risk of breast cancer and, when progestogens are taken fewer than 10 days per month, endometrial cancer.

Consider risks and benefits of hormonal products and use only under careful medical supervision
This new information about cancer risks – and also protection against cancer in the case of oral contraceptives – makes it important that each woman who uses these hormonal products discuss the risks and benefits with her doctor, taking into consideration her personal circumstances and family history of cancer and other diseases.

ABOUT THE IARC MONOGRAPHS

What are the IARC Monographs?
The IARC Monographs critically review and evaluate the published scientific evidence on human carcinogenic hazards. These include chemicals, complex mixtures, occupational exposures, lifestyle factors, and physical and biological agents. International, interdisciplinary working groups of expert scientists prepare the critical reviews and consensus evaluations. Nearly 400 potentially carcinogenic agents and exposures have been identified in the 91 volumes and approximately 900 evaluations developed since 1971. National and international health agencies

use the IARC Monographs as a source of scientific information and as the scientific basis for their efforts to prevent cancer.

Definitions

- Group 1: The agent (mixture) is carcinogenic to humans.
  The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

- Group 2

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

- Group 2A: The agent (mixture) is probably carcinogenic to humans.
  The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

- Group 2B: The agent (mixture) is possibly carcinogenic to humans.
  The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

- Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents, mixtures and exposure circumstances for which the *evidence of carcinogenicity is inadequate* in humans and *inadequate or limited* in experimental animals
Exceptionally, agents (mixtures) for which the *evidence of carcinogenicity is inadequate* in

humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

- Group 4: The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

FOR FURTHER INFORMATION

Contact Dr Nicolas Gaudin, Chief of IARC Communications, at com@iarc.frcom@iarc.fr . The Working Group's summary on this topic will soon appear on the IARC Monographs website (http://monographs.iarc.fr). More details available in the August issue of The Lancet Oncology (http://www.thelancet.com/journals/lanonc/issue/current).

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